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TOXICOLOGY OF ATMOSPHERIC SULFUR DIOXIDE DECAY PRODUCTS

Trent R. Lewis, et al

National Environmental Research Center
Research Triangle Park, North Carolina

July 1972

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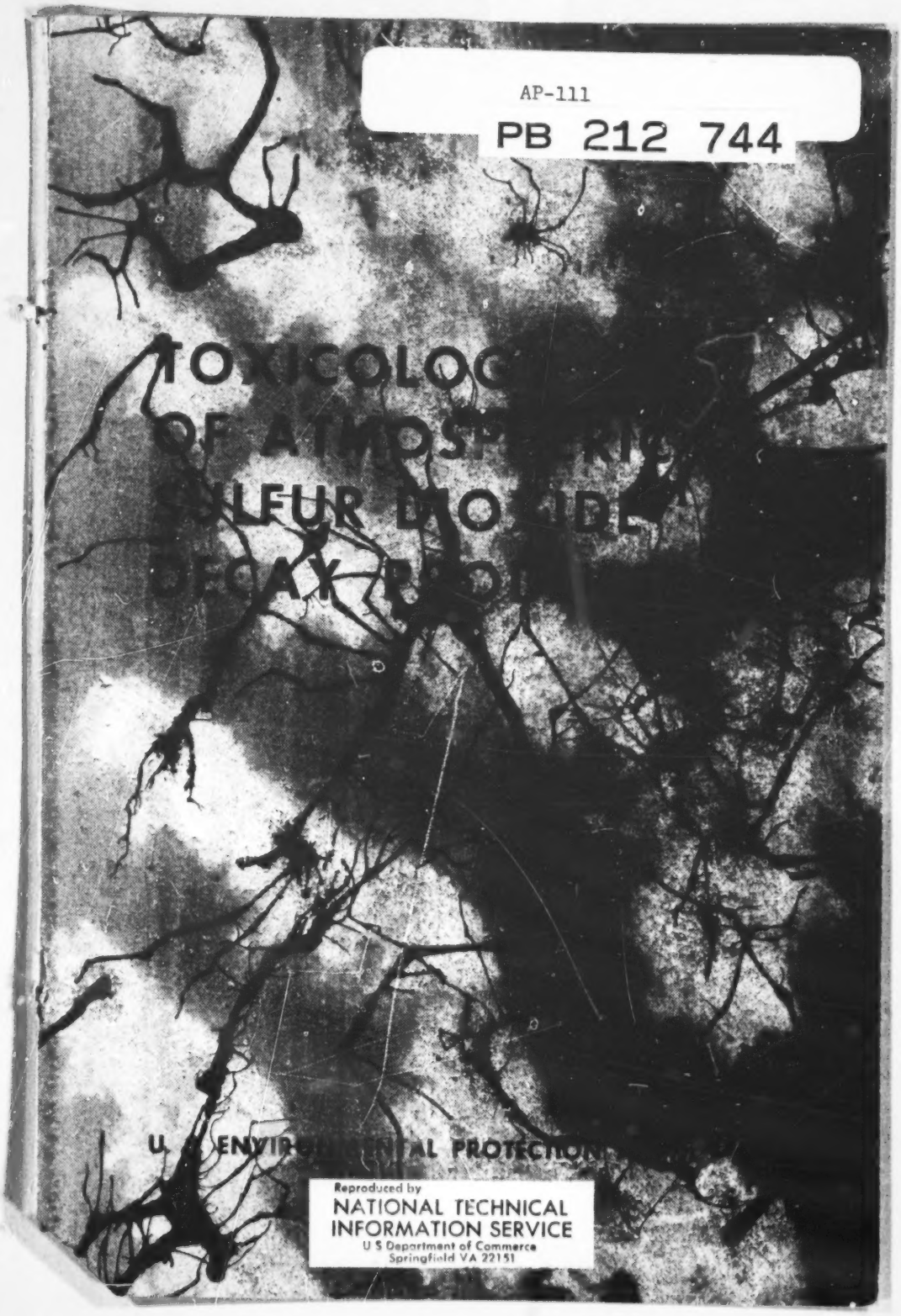
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Studies of atmospheric chemistry have shown that under certain conditions sulfur dioxide can be converted to sulfuric acid and particulate sulfates. Air quality criteria and standards for sulfur dioxide should, therefore, take into account the irritant potency of these oxidation products, recognizing that both sulfur dioxide and its degradation products can react further with other air pollutant constituents. The document reviews (1) toxicity studies conducted in experimental animals, and (2) toxicity studies involving human subjects. The data presented on animal studies examines the effect of sulfuric acid mist particle size and exposure duration on mortality and pathology studies. It also reviews the findings of related studies of pulmonary function. The review presents, from human studies, data which discusses subjective and physiological responses to irritative properties of sulfuric acid mist, and sensory and central nervous system responses to sulfuric acid mist.

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Trent R. Lewis, Mary O. Amdur,
Martin D. Fritzhand,
and
Kirby I. Campbell

Division of Health Effects Research

ENVIRONMENTAL PROTECTION AGENCY
National Environmental Research Center
Research Triangle Park, North Carolina
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Other factors that affect the toxicity of particulate oxidation products of sulfur dioxide, such as retention, site of deposition, hygroscopic nature of the products, and the subject's breathing pattern are discussed.

Key Words: toxicology, air pollution, sulfuric acid, sulfates, human, animal, respiratory, neurosensory

TOXICOLOGY OF ATMOSPHERIC SULFUR DIOXIDE DECAY PRODUCTS

INTRODUCTION

Studies of atmospheric chemistry have shown that a portion of the sulfur dioxide (SO_2) emitted into the atmosphere undergoes oxidation, leading, eventually, to the formation of sulfuric acid (H_2SO_4) and sulfate particulates. Studies in experimental toxicology demonstrate that some of these particulate oxidation products have a greater irritant potential than sulfur dioxide itself. Clearly then, air quality standards for sulfur dioxide should be set with due consideration for the potential sulfur dioxide has, under certain atmospheric conditions, for forming its more hazardous derivatives.

The acute air pollution episodes that occurred in Donora, Pennsylvania, and London, England, precipitated intensive research into the toxicological and physiological effects of sulfur dioxide and certain of its decay products. In spite of this research, most of which was conducted between 1950 and 1963, many questions regarding health problems related to atmospheric oxides of sulfur remain unanswered. To consolidate the information that is available, this report presents a review of the literature on the toxicology of some of the sulfur dioxide decay products, and, in one section, presents recent data on the comparative toxicity of those decay products.

TOXICITY IN EXPERIMENTAL ANIMALS

STUDIES OF MORTALITY AND PATHOLOGY

Experimental studies that use mortality and pathology as the criteria of response by necessity involve the exposure of animals to pollutant concentrations far above those occurring in the atmosphere in order to produce measurable effects. Data from such studies cannot, without some misgivings, be extrapolated to give practical guidance in setting safe levels for those air pollutants. Such studies, however, are usually the initial step in investigating the toxicity of a substance.

Considerable species differences have been observed in the response of small laboratory animals exposed to sulfuric acid mist. Treon et al.[1] exposed small numbers of several species to H_2SO_4 mist, 95 percent of the particles of which were smaller than 2 micrometers (μm) in diameter. Using concentrations ranging from 87 to 1600 milligrams per cubic meter (mg/m^3), they found increasing sensitivity as shown: rabbits < rats < mice < guinea pigs. Guinea pigs died of exposures not lethal for other species; when exposed to concentrations sublethal to them, they had proportionately greater respiratory irritation and lung pathology than the other species studied. The results of Mathur[2] also corroborated that guinea pigs are less resistant than mice to sulfuric acid mist.

Sulfuric Acid Mist Particle Size

Questioning the influence of aerosol particle size on response, Amdur et al.[3] began by determining the 8-hour LC_{50}* of sulfuric acid particles with a mass median diameter (MMD) of 1 μm. The LC_{50} was 18 mg/m^3 for 1- to 2-month-old guinea pigs and 50 mg/m^3 for 18-month-old animals. In subsequent studies, sulfuric acid mists of 2.7-μm-MMD particles proved more toxic than those of 0.8-μm-MMD particles and

*LC_{50} is the concentration lethal for 50 percent of the experimental population.

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the smaller material was more toxic at 0° C than at room temperature.[4] These data indicate that the age of the animal, particle size, and temperature all influence lethality.

Other variables have been found to influence the toxicity of sulfuric acid: the presence of smoke[4] resulted in increased mortality and the presence of aerosolized ammonium carbonate[5] diminished the effects of the acid. The increase in mortality was attributed to the larger size of the toxic particles, which resulted from the adsorption of the acid upon the smoke particles. The decrease in effects was attributed to chemical neutralization of the sulfuric acid.

Amdur et al.[3] and Pattle et al.[5] both examined the gross and microscopic pathology of the lungs of exposed guinea pigs and agreed in their findings. Animals that died after exposures to H_2SO_4 of less than 2 hours had grossly distended and emphysematous lungs, but no other serious lesions.[5] The cause of death appeared to be asphyxiation caused by bronchoconstriction and laryngeal spasm. The lungs of animals that died after longer exposures had gross pathological lesions, including capillary engorgement and hemorrhage.[3,5] It has been suggested that these changes represent sequelae to the combined effects of anoxia and increased intrathoracic pressure caused by bronchoconstriction and laryngeal spasm.[5] The lungs of animals that survived the longer exposures showed spotty areas of old hemorrhage and some areas of consolidation, especially around the hilar regions. Although such exposures do not give rise to death, during or afterwards, the damage is repaired only very slowly.

Amdur et al.[3] reported that, when the H_2SO_4 concentration was 8 mg/m^3, extending the exposure time to 72 hours did not increase mortality beyond the amount observed in 8-hour exposures. Pathological examination of the lungs, however, revealed that the longer exposures greatly increased the damage. In the 8-hour exposures, damage was limited to thickening of the alveolar walls and consolidation of lung tissue (CT*=64 mg/m^3-hr). In animals exposed for 72 hours (CT=576 mg/m^3-hr), damage was greatly enhanced. These workers postulated

*CT is the product of time and concentration.

that sulfuric acid mist has two distinct toxic actions. It promotes laryngeal and bronchial spasms, causing immediate death by an action related primarily to concentration and individual sensitivity, and it also produces parenchymal lung damage, an effect that is more dependent upon total dosage. Pattle et al.[5] pointed out that the lung damage probably results from the direct irritant action of acid mist deposited on the lung tissue and that such deposition and irritation may be the mechanism by which the mist causes death in animals more resistant to bronchial-laryngeal spasm than the guinea pig. This mechanism may account, as well, for many of the marked differences in mortality observed by early investigators who used different exposure concentrations.

Exposure Duration

Thomas et al.[6] exposed guinea pigs to sulfuric acid mist for periods of 18 to 140 days. They used three particle sizes (0.6, 0.9, and 9.0 μm) in concentrations of 4 mg/m^3 or less, except for occasional accidental higher exposures. The coarse particles produced lesions in the upper respiratory tract and slight edema in the larynx and trachea, with less mucus in the major bronchi. The mists composed of 0.9-μm particles produced greater lung damage than either the 0.6- or 9.0-μm particles. Exposure of young animals to 0.9-μm mists produced slightly edematous lungs and, rarely, capillary hemorrhage. Some increase in desquamated epithelial cells was observed in the minor but not in the major bronchi; the epithelium appeared intact. Major and minor bronchi both had less mucus than controls. The authors concluded that the guinea pig could tolerate continuous exposure to levels of about 2 mg/m^3 sulfuric acid mist for more than 3 months with only minor effects.

Bushtueva[7,8] exposed guinea pigs to 2 mg/m^3 sulfuric acid mist of unspecified particle size for 5 days. The animals developed edema and thickening of alveolar walls. Exposures to 1 mg/m^3 for 1 to 2 weeks produced slight catarrh in the mucous membranes of the trachea and bronchi, and slightly defined but widely distributed interstitial proliferation accompanied by round-lymphoid-cell infiltration around the

blood vessels and bronchi. These latter changes seemed to be progressive, for they were more highly developed 2 to 3 months after exposure. A concentration of 0.5 mg/m^3 produced only a slight "lung irritation."

Conclusions

Sulfuric acid is a respiratory irritant, and, when present in sufficient concentration, it will cause the death of exposed animals. The guinea pig is the most sensitive species among the common small laboratory animals, followed in decreasing order by mice, rats, and rabbits. The guinea pig's greater sensitivity probably results from its greater susceptibility to bronchial and laryngeal spasm. Although the enhanced sensitivity makes this animal useful for some studies of the irritant potential of low concentrations of sulfuric acid, the results must be applied judiciously when extrapolation is made to the effects of sulfuric acid air pollution on human health. In all cases, concentration has been shown to be a more important factor in sulfuric acid-produced death than duration of exposure.

Sulfuric acid also causes pathological lesions in the lungs after much less than lethal exposures. Effective, short exposures (up to 72 hours) produce a degree of lung damage related to the arithmetic product of concentration and time (CT) rather than to the concentration alone. Such damage is slow to repair. The fact that concentrations below 2 mg/m^3 produce only minor lung damage after extended exposures (about 3 months) indicates that the CT-damage relationship observed in 8- and 72-hour exposures cannot be extrapolated directly to long-term effects of low concentrations.

Data clearly indicate that the particle size of sulfuric acid mist is also an important factor in determining its irritant potency. When the criterion was mortality resulting from an 8-hour exposure, a mist of larger particles (2.7 μm versus 0.8 μm) was more toxic. When pathological lesions resulting from long-term exposures were the criterion of response, the effect of 0.9-μm particles was greater than that of either 0.6- or 9.0-μm particles. The effect of particle size will be discussed further in the next section.

STUDIES OF PULMONARY FUNCTION

Methods like the ones discussed in this section can be used to evaluate the effects of low concentrations of irritants that do not usually produce lung damage or cause death. In other words, they can be used to examine the response of experimental animals to air pollutants at concentrations known to occur in urban atmospheres.

Sulfuric Acid Mist Particle Size

Employing unanesthetized and spontaneously breathing guinea pigs, Amdur[9-11] measured the effect of sulfuric acid mist on pulmonary function by the following parameters: flow resistance of the lungs and airways; compliance (a measure of the elasticity of the lungs); tidal volume (the volume of each breath); respiratory frequency; and minute volume (tidal volume times respiratory rate). These data also permitted her to make rough estimates of elastic-resistive work and the total work of breathing.

Amdur used concentrations ranging from 2 to 40 mg/m^3 and particles of 0.8, 2.5, and 7.0 μm (MMD). Experimental results indicated that the size of particles in the aerosol is critical to both the nature and degree of the irritant response elicited. Results of these experiments made clear that data obtained from exposure to high concentrations could not have been extrapolated to indicate, in a valid manner, the reaction to lower concentrations , since irritant potency varied with both concentration and particle size of the sulfuric acid mist. This fact underlines the need for, and the importance of, methods that can directly assess responses to low concentrations of irritants.

The 7.0-μm-MMD particles, at a concentration of 30 mg/m^3, produced a statistically significant increase in flow resistance but no other detectable changes in respiration. Few particles of this size would be expected to penetrate beyond the nasal passages, so that the observed increase in flow resistance was probably restricted to the upper respiratory tract, especially since the other parameters measured were not altered.

The 0.8-μm-MMD particles produced an increase in resistance, accompanied by a proportionally lesser decrease in compliance, an increase in elastic and resistive work, and, hence, an increase in the total work of breathing. These changes were statistically significant at the lowest concentration tested (1.9 mg/m^3). Onset of response was prompt and resembled the pattern of changes observed after inhalation of sulfur dioxide. Changes in pulmonary function such as these are consistent with narrow air passages caused by bronchoconstriction, mucosal swelling, or increased mucosal secretion.

The 2.5-μm-MMD particles also increased flow resistance at all concentrations examined (2.3 to 44 mg/m^3). The relative toxicity of the 0.8- and 2.5-μm-MMD particles, evaluated by increased pulmonary flow resistance, was highly dependent upon concentration; however, at high concentrations, the larger particles elicited a much greater response, whereas at low concentrations the smaller particles gave the greater response, again demonstrating that data obtained from exposures to high concentrations could not be used to predict accurately the responses to low concentrations. The increased toxicity of 2.5-μm- as compared with 0.8-μm-MMD particles at high concentrations confirmed the earlier finding of Pattle et al.[4]

Further comparison of data for the two particle sizes suggested a difference in physiological action, presumably related to the site where the particles were deposited in the respiratory system. Response to the 2.5-μm-MMD particles, but not to the 0.8-μm-MMD particles, was slow to develop, occurring only after 40 to 45 minutes of exposure. This delay suggested the possibility that the different responses were mediated by different mechanisms, a possibility that was confirmed both by the nature of the changes in the mechanical properties and by the post-mortem appearance of the lungs.

The alterations in mechanical properties that occurred indicated that large sulfuric acid particles produced a complete obstruction of some air passages, whereas small particles caused a narrowing of the airways but not complete obstruction. The gross pathology of the lungs

was consistent with data derived from pulmonary function tests. Animals exposed to the high concentration of 2.5-μm-MMD particles developed extensive areas of atelectasis, frequently involving whole lobes. In addition, their lungs were edematous, as demonstrated by a significant increase in the ratio of lung weight to body weight. These findings suggested that high concentrations of larger particles, which probably are deposited in the vicinity of the major bronchi, produce severe local irritation of the larger air passages and cause swelling and increased exudation of fluid, which eventually lead to complete obstruction.

The pulmonary flow-resistance values were slow to return to pre-exposure levels after the end of a 1-hour exposure. Animals exposed to 15 mg/m^3 or more still showed elevated resistance 2 hours after exposure had ended. This slow return to normal has been found consistently after exposure to irritant aerosols or to the combination of irritant gas and inert particulate material.[12,13] The reasonable explanation for the slower recovery from exposure to an aerosol as opposed to an irritant gas is apparently the fact that the particles, having been deposited on the respiratory tract, continue to exert their irritant effect. The irritant gases, on the other hand, are cleared from the lung when exposure ceases, and the respiratory system returns to normal functioning rather rapidly unless the exposure concentration has been extremely high. The enhancement that results from combining inert aerosols and irritant gases appears to be mediated through the formation of an irritant aerosol,[12,13] which could account for the prolonged response to such exposures.

Lewis et al.[14,15] studied the effects of chronic H_2SO_4-aerosol exposure on canine pulmonary function. Animals were exposed for 621 days to 0.5-μm-MMD H_2SO_4 particles, at a concentration of 0.8 mg/m^3, and pulmonary function tests were performed 225 days and 621 days following the onset of exposure. At 225 days, diffusion capacity had decreased. After 621 days of exposure, average carbon monoxide diffusion capacity and residual lung volume were reduced and

total pulmonary resistance was increased. Post-mortem examination showed that the net lung volume was reduced.

Sulfur-Containing Particulate Aerosols

Amdur and Corn[16] studied the irritant potency of zinc ammonium sulfate, zinc sulfate, and ammonium sulfate, and found a difference in the potencies as judged by increases in flow resistance resulting from exposure to 1 mg/m^3 concentrations having an MMD particle size of 0.29 μm.

Zinc sulfate exhibited about half the irritant potency of zinc ammonium sulfate. Ammonium sulfate was the least irritant of the three compounds, producing a response about one-third to one-fourth that observed from exposure to an equal concentration of zinc ammonium sulfate.

In further studies of the effect of particle size on the irritant potency of zinc ammonium sulfate, four MMD sizes were used: 0.29, 0.51, 0.74, and 1.40 μm. Concentrations ranged from 0.25 to 3.60 mg/m^3. Figure 1 shows the results obtained when the concentration of aerosol was held constant at about 1 mg/m^3 and the particle size was varied. Particle size by weight is indicated in micrometers. This method for calculating mass-size is explained by Amdur and Corn.[16] From the curve it is evident that the irritant potency, as judged by the increase in flow resistance produced by the 1-hour exposure, increased as the particle size decreased over the range of sizes examined. Amdur and Corn[16] concluded that the greater irritant potency of the smaller particles could represent the reaction to an increased number of pinpoint stimuli produced by the greater number of particles present in the more finely dispersed material; to the differing depth of penetration into the peripheral areas of the lung; or to a combination of these factors.

From data available for several concentrations of zinc ammonium sulfate at various particle sizes, Amdur and Corn prepared a family of dose-response curves. As Figure 2 shows, not only was the response

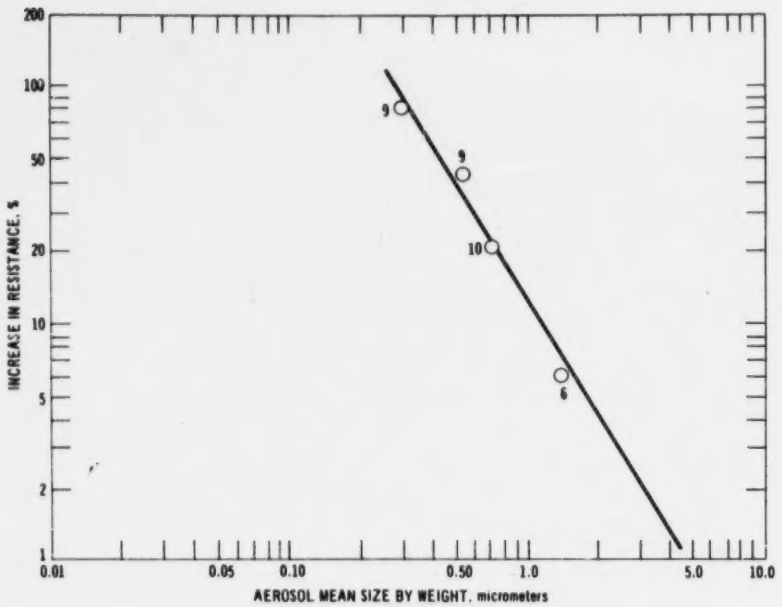

Figure 1. Effect of particle size on airway response to 1 mg/ m^3 zinc ammonium sulfate aerosol. Numerals beside each point indicate number of animals. Data and calculation of mean size by weight from Amdur and Corn.[16]

to a given concentration greater as the particle size decreased, but the slope of the dose-response curves was also steeper. This means that a small increase in mass concentration produced a larger increment in biological response as the particle size decreased, re-emphasizing the fact that if a compound is dispersed as particulate material a measure of mass concentration alone is not sufficient to permit useful assessment of its irritant potency.

Nadel et al.[17] studied the effect of aerosols of histamine and of zinc ammonium sulfate on anesthetized, artificially ventilated cats. The aerosols were submicrometer in size and the concentrations of zinc ammonium sulfate were 40 to 50 mg/m^3. The sulfate aerosol produced a physiological response similar to that produced by histamine, but lesser in degree. The response to a 3-minute inhalation included increased pulmonary resistance, decreased pulmonary compliance, and increased end-expiratory transpulmonary pressure. As

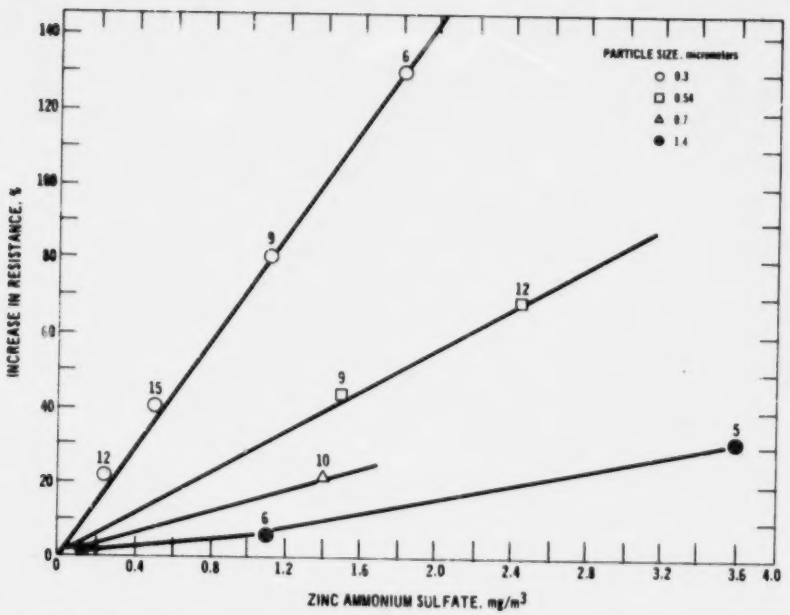

Figure 2. Dose-response curve of zinc ammonium sulfate aerosol for different particle sizes. Numerals beside each point indicate number of animals. Data from Amdur and Corn.[16]

correlation with the physiological studies, the authors made anatomical studies after rapidly freezing the lungs in the open chest. These showed that bronchioles up to 400 μm were narrower in exposed than in control animals and that the mucosa was longitudinally furrowed. Bronchi and bronchioles larger than 400 μm were not significantly different from controls. The authors noted the similarity between the action of histamine and of zinc ammonium sulfate aerosol. In regard to extrapolating the results they concluded, "It remains to be demonstrated that acute changes reported here at aerosol concentrations of 40 to 50 mg/m^3 are exaggerated but similar in nature to those produced, if any, at lower concentrations".[17] Follow-up work is clearly needed in this field.

In the course of examining the effect of aerosols on response to sulfur dioxide, Amdur and Underhill[18] examined the irritant potency of several other sulfates. They reported that 1 mg/m^3 ferric sulfate

[$Fe_2(SO_4)_3$] produced a 77-percent increase in flow resistance during a 1-hour exposure, which would definitely indicate that this substance is an irritant. On the other hand, ferrous sulfate ($FeSO_4$) and manganese sulfate ($MnSO_4$) at the same concentration produced no detectable alteration in resistance. Not all sulfates, then, are irritant in nature, and the sulfate ion per se is not known to have irritant potency.

Particulates in Combination with Sulfur Dioxide

Because data from atmospheric chemistry studies have indicated that sulfuric acid and particulate sulfates are formed from sulfur dioxide emitted to the atmosphere, it is essential that the comparative irritant potency of sulfur dioxide gas and its chemical reaction products be examined. A long-term research program undertaken by Amdur et al. has provided data on the effects of sulfur dioxide gas and several particulate oxidation products on the guinea pig. The authors are using the same physiological techniques for all the pollutants, which permits direct comparison of the irritant potency of these compounds. Their data[19] are summarized in Figure 3.

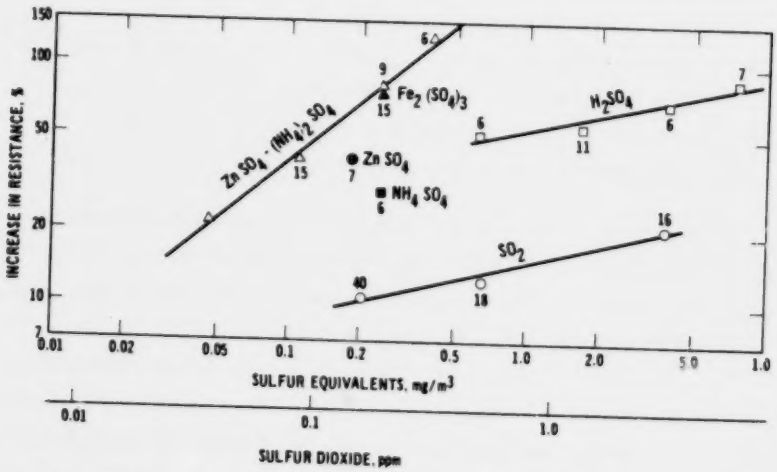

Figure 3. Comparison of irritant potency of sulfur dioxide and sulfur-containing particulates. Numerals beside each point indicate number of animals. Data from Amdur.[19]

Even a casual glance indicates clearly that an equivalent amount of sulfur present as sulfur dioxide gas produces a lesser irritant response than either the particulate sulfates or sulfuric acid. One part per million of SO_2 is the equivalent of 1.3 mg S/m^3. When present as sulfur dioxide gas, this amount of sulfur increases flow resistance by about 15 percent. If, through reaction in the atmosphere, this sulfur equivalent were converted to 0.7-μm-MMD sulfuric acid mist, it could produce an increase in resistance of about 60 percent, a fourfold potentiation of irritant response. If, on the other hand, that same amount of sulfur were converted to zinc ammonium sulfate particles of 0.3-μm MMD, resistance would increase about 300 percent, a twentyfold potentiation. Such complete conversion in the atmosphere is of course highly unlikely, but an oxidation of 10 percent can occur readily. Ten percent of 1 ppm sulfur dioxide has an equivalent sulfur content of 0.13 mg/m^3, and if this were present as an irritant sulfate with a particle size of 0.3 μm, it would increase flow resistance about 45 percent. If the response to the particulate sulfate and the response to the remaining sulfur dioxide (which increased resistance about 15 percent) were purely additive, one could estimate a total increase in pulmonary flow resistance of approximately 60 percent, an important fourfold potentiation in irritant response. The response to such combinations is more than additive,[16,20] however, so that the overall irritant effect would be even greater than these figures indicate. These data clearly suggest that a toxicological response to sulfur dioxide gas alone is not a sufficient basis for assessing its role in air pollution.

The overall problem of the effect of inert aerosols on physiological responses to irritant gases will not be discussed in detail here. It has been reviewed in the air quality criteria documents for both sulfur oxides[21] and particulate material,[22] and is discussed in a recent review by Amdur.[23] Amdur and Underhill[18] reported the results of a study on the effects of various aerosols on the response to sulfur dioxide gas. Their findings indicated that the degree to which the response to sulfur dioxide was potentiated by an aerosol was determined by the solubility of sulfur dioxide in the liquid droplet and by the extent to

which it was oxidized to sulfuric acid. The importance of solubility was suggested by the fact that the potentiating ability of aerosols of sodium chloride, potassium chloride, and ammonium thiocyanate could be related, in a reasonable manner, to the solubility of sulfur dioxide in solutions of these salts. Further evidence for the role of solubility came from the observation that none of the various solid, dry aerosols that were tested potentiated the response to sulfur dioxide. These included spectrographic carbon, activated coconut charcoal, iron oxide fume, triphenyl phosphate, fly ash, and manganese dioxide. None of these substances, at concentrations of 8 mg/m^3 or above, produced a detectable effect on pulmonary flow resistance or potentiated response to levels of sulfur dioxide ranging from 1 to 100 ppm. In contrast, aerosols of soluble salts of ferrous iron, manganese, or vanadium at concentrations of 0.7 to 1 mg/m^3 potentiated response to sulfur dioxide about threefold. At significant humidity levels like those in the respiratory tract, these substances would not only form droplets, but would also absorb sulfur dioxide; they are known to be agents that favor the oxidation of sulfur dioxide to the more potent sulfuric acid. The properties of these and other sulfur compounds have been studied thoroughly by many researchers, who have found that the toxicity of the compounds is directly related to the metal ion itself rather than to the attached sulfur radical. These compounds will not be reviewed here, but a relevant bibliography is appended.

Hygroscopic Properties of Sulfuric Acid

Another toxicologic aspect of sulfuric acid aerosol inhalation is related to its hygroscopic nature. Even when sulfuric acid particles are inhaled in relatively dry air, they will expand within the respiratory system by water absorption because inspired ambient air becomes saturated with water drawn through the nose, mouth, and pharynx. Since large particles are retained with greater efficiency, more hygroscopic particles, such as sulfuric acid and water-soluble sulfate aerosols, are deposited than non-hygroscopic materials of the same size. Depending on other factors, physiologic response may, but need not, be enhanced

in proportion to the increase in percentage retained because of expansion in situ.

In the case of hygroscopic aerosols, the original size of the parent particle will also determine the subsequent size of the hydrated particle, and, hence, the site of its retention along the respiratory system. Larger particles will have a tendency to be trapped along the upper respiratory airways (nasopharnygeal), where their relative toxicity is usually lessened and from which removal is more rapid. Increases in particulate size from the nares to the alveoli are difficult to quantitate in vivo; therefore, studies of the effects of hygroscopic particles have been limited largely to empirical models, in which alterations in, or potentiation of, physiologic responses are related to variations in physicochemical properties of the particulate matter; for example, size, chemical composition, solubility, catalytic convertibility, and moisture absorbability.

When interpreting physiologic responses to aerosols of a sulfurous nature, assessing their toxic potential, and relating aerosols to models of respiratory deposition, one must not lose sight of the fact that these phenomena are influenced by the hygroscopic nature of the particles.

Conclusions

The studies discussed above cannot be extrapolated simply and directly to predict the human response to particular substances. They do provide useful information regarding the nature of mechanisms by which effects are produced; however, they may lend more insight into responses of the sensitive segment rather than of the robust healthy segment of the population.

For practical considerations in using these experiments as indirect guidance in air pollution research, two critical points emerge. The first is the extreme importance of the particle size to the irritant potency of particulate products of sulfur dioxide. The most important size is in the submicron range. Data on mass concentration alone provide an insufficient basis for predicting irritant potency of particulate products of sulfur dioxide.

The second important point is that the particulate oxidation products of sulfur dioxide generally have much greater irritant potency than the parent sulfur dioxide gas, as indicated by the comparative data in Figure 3 as well as by increased response to sulfur dioxide in the presence of particulate material known to dissolve the gas and/or catalyze its conversion to sulfuric acid or sulfates. Particle sizes of oxidative products of sulfur dioxide are, in part, affected by the hygroscopic properties of the products; consequently, physiologic responses and pulmonary deposition of inhaled particulates may be significantly altered by moisture in the atmosphere and within the respiratory tract. Atmospheric levels of sulfur dioxide and their health implications should therefore be assessed in terms of the potential for formation of more irritant substances. To do otherwise is to miss the toxicological point and seriously becloud important issues.

TOXICITY IN MAN

Only limited research has been done on the effects of sulfuric acid on human pulmonary function, and none on the effects on man of the various sulfates that have irritant potency for the guinea pig. Studies that regard both physiological methodology and characterization of the aerosol particle size with meticulous attention are badly needed. The exposure of human volunteers to low concentrations of H_2SO_4 mist, to define its toxicological effects, has involved two divergent, though complementary, branches of research. One branch has concerned itself with the effects of H_2SO_4 aerosols upon the normal physiological responses of the central nervous system: the role of H_2SO_4 mist and its interrelationship with sensory modalities and cerebral cortical function. These studies are reported exclusively in the Russian literature. The other branch of research has been concerned primarily with the irritative effects of H_2SO_4 aerosols and the changes in respiratory function that occur subsequent to exposure to concentrations that approximate the allowable industrial standards set by the governments of the United States[24,25] and the Union of Soviet Socialist Republics.[26]

STUDIES OF SUBJECTIVE AND PHYSIOLOGICAL RESPONSES TO IRRITATIVE PROPERTIES OF SULFURIC ACID MIST

Detection by Subjects

In 1913, Dorsch[27] studied workers in the battery room of a German telephone exchange. He found that H_2SO_4 mist was only rarely detected by the employees when the concentration was below 0.5 mg/m^3. They complained of slight nose and throat irritation at 2.0 mg/m^3, distinct discomfort at 3 to 4 mg/m^3, and marked discomfort when the concentration rose to 6.8 mg H_2SO_4/m^3. Bushtueva[28] exposed ten volunteers to H_2SO_4 aerosols with the following results. When exposed to concentrations less than 1.1 mg/m^3, the volunteers compained of ticklish, scratchy throats; when exposed to levels ranging from 1.1 to 2.4 mg/m^3, all subjects noticed considerable

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irritation at the base of the esophagus and 40 percent of them experienced some irritation of the eye mucosa. When the aerosol level was raised to 2.4 to 6.0 mg/m^3, all subjects experienced acute irritation of the mucous membranes, a pronounced reflex cough, and irritation of the eye mucosa. The threshold concentration was approximately 0.7 mg/m^3 (0.60 to 0.85 mg/m^3). In that study, the particle size of the acid mist was not stated. Amdur[29] was unable to detect responses in subjects exposed to aerosol levels less than 1 mg/m^3, using odor, taste, or irritancy as parameters, although all 15 of her subjects detected the aerosol when the level was raised to 3 mg/m^3, noting that it "felt like breathing dusty air." Some subjects found 5 mg/m^3 very objectionable, but others less so, and, for all subjects, a deep breath of this concentration usually produced coughing. In another study, Bushtueva[30] found that the presence of 0.· mg H_2SO_4/m^3, even when combined with 1 mg SO_2/m^3, was below the sensitivity threshold of all subjects. The fact that the results reported in each of these papers are remarkably similar to Dorsch's[27] original description of H_2SO_4 mist irritancy, indicates that the dose-response curve for human beings has remained quite stable during the past 60 years of experimentation and, in contrast to animal data, appears to be physiologically predictable in almost all instances.

Effects of Humidity, Acidity, and Particle Size on Subject Response

Sim[31] studied the response of healthy males, aged 18 to 46, to H_2SO_4 mist. He noted that at a given concentration a mist of larger particle size and lower acidity, produced under conditions of high humidity, was more irritant than a mist produced under lower humidity at the same concentration, but with smaller particles and higher acidity. Pulmonary air-flow resistance was 35 to 100 percent greater than normal when the volunteers were exposed to a 10N H_2SO_4 aerosol of 1-μm-MMD particles at a concentration of 39 mg H_2SO_4/m^3, a temperature of 18.4° C, and humidity of 61 percent. Altering the aerosol to 25° C, 91 percent humidity, acidity of 4N H_2SO_4, and particle size of 1.5 μm evoked intense coughing, lacrimation, and

rhinorrhea, which continued throughout the exposure. Coughing decreased somewhat after the first 10 minutes of exposure and airway resistance ranged from 43 to 150 percent greater than normal. Adding magnesium oxide particulate to the exposure air did not alter the irritancy, although addition of ammonia toward the end of the H_2SO_4 exposure resulted in rapid and complete disappearance of all symptoms, thus corroborating Pattle's[5] observations on guinea pigs. Toyama[33] also correlated airway resistance with particle size. In an aerosol of 4.6-μm particles, a mist concentration of 0.8 to 1.4 mg/m^3 increased airway resistance 36.5 percent in 24 healthy males; as an aerosol of 1.8-μm particles, a mist concentration of 0.01 to 0.1 mg/m^3 increased airway resistance 17.9 percent. The latter concentrations appear questionable, since 0.01 to 0.1 mg H_2SO_4/m^3 are concentrations far below the reported thresholds for <u>any</u> physiological response.

Hamilton[32] stated in 1948 that the site of action for H_2SO_4 fumes is the upper respiratory tract, "that this action is not severe, and that no instance of bronchitis [is]...traceable to such fumes." Sim[31] described, however, how he, himself, became increasingly sensitive to the mist during 10 months of exposure, developing a moderately severe but extremely persistent bronchitis, which immediately exacerbated into uncomfortable periods of coughing and wheezing that occurred whenever he was exposed to H_2SO_4 mist.

Effects of Sulfuric Acid Mist on Respiratory Retention

Apparent increases in the respiratory rate of human subjects exposed to H_2SO_4 irritant were described in reports by Bushtueva,[28] Sim,[31] and Amdur.[29] The increase is not suprising, for Wilson[34] in 1948 showed that the retention of inhaled aerosol particles decreased as the respiratory rate increased. Morando[35] briefly (for 15 minutes) exposed normal human subjects not accustomed to inhaling H_2SO_4 fumes to concentrations varying from 0.35 to 5.0 mg/m^3. Even at concentrations not subjectively detected by the volunteers (less than 0.5 to 0.7 mg/m^3), the respiratory rate increased rapidly and remained

elevated for several minutes after exposure. Amdur[29] exposed fifteen subjects to 0.35 to 0.5 mg/m^3 and noted that the respiratory rate increased about 30 percent above control values; the maximum inspiratory and expiratory flow rates decreased by about 20 percent; and tidal volume increased by about 28 percent. These changes occurred during the first 3 minutes of exposure and were maintained throughout the 15-minute exposure period. Values returned to pre-exposure levels within 15 minutes after the exposure ended. During the first minute after exposure, the tidal volume rose above and then declined to control levels.

These experiments do not provide the physiological evidence necessary to indicate conclusively that bronchoconstriction was the response to H_2SO_4 mist, although the data suggest that this was the case. Bushtueva[28] found clear-cut reflex changes in respiratory rhythm and amplitude when she gave volunteers multiple exposures to an H_2SO_4 mist of 1.8 to 2.0 mg/m^3. At concentrations of 1.0 to 1.1 mg/m^3, changes in respiration were also noted, though rhythm and amplitude were decidely lower. She was unable to demonstrate respiratory changes when the mist concentration was below 1.0 mg/m^3, but this inability may have reflected differences in the degree of "aerosol dispersion."

As the respiratory rate increases, the percentage of H_2SO_4 mist retained by the respiratory tract is definitely reduced. The change in respiratory rhythm and amplitude may be a reflex protective mechanism that prevents the retention of the irritant,[29, 34] thereby decreasing its toxic effects. By measuring the total volume of air breathed, and the concentration of the H_2SO_4 aerosol in the mixing chamber and in exhaled air, Amdur[29] was able to show that average retention of inhaled H_2SO_4 varied from 50 to 87 percent with exposure concentrations of 0.4 to 1.0 mg/m^3. She gave two possible reasons for such relatively high retention. First, the aerosol levels used in the experiment increased the respiratory rate by only 35 percent (5 to 7 breaths per minute), certainly not enough to reduce retention far below baseline values; and, second, the strong affinity of H_2SO_4 droplets for moist surfaces, such as the mucous membranes of the respiratory tract, *may have enhanced retention.*

As noted earlier, the respiratory rate and pulmonary air-flow resistance of human volunteers rose rapidly as exposure concentrations of H_2SO_4 aerosol were increased. Symptomatically, bronchospasm was also evident in the healthy subjects, presenting a kaleidoscopic picture of wheezing, increased secretions, dyspnea, spasmodic coughing, and occasional chest pains. The intensity and combinations of the symptoms depended upon the aerosol concentration and length of exposure.[36] Two observer-subjects[31] reported occurrence of chronic bronchitis during long-term intermittent exposure to H_2SO_4 aerosol.

Bronchospasm, increased upper-respiratory-tract secretions, and a rapid respiratory rate were consistently found, along with elevated pulmonary air-flow resistance, in volunteers exposed to mist levels greater than 0.35 to 0.5 mg/m^3. All of the subjects involved in previous experiments were young healthy adults who could easily compensate for the increased resistance imposed on their breathing. Elevated airway resistance severely embarrasses breathing in individuals already burdened by cardiorespiratory deficiencies, however, making it more difficult to obtain needed oxygen. Moreover, bronchospasms and increases in secretory and respiratory rates impair gaseous exchange in the lungs, and carbon dioxide accumulates, which causes respiratory acidosis. An acidotic condition superimposed on a restricted oxygen intake explains many of the effects seen in pulmonary cripples when they are exposed to rapidly rising concentrations of H_2SO_4 aerosols, above threshold levels.[37]

Conclusions

Research data concerning the effects of aerosol particle size, temperature, or humidity on the human response to H_2SO_4 mist exposure are scarce. The few long-term human-exposure studies have been limited, essentially, to epidemiological surveys. Ethical considerations preclude achieving the requirements of controlled long-term, experimental, human exposure as such. Intensive industrial-exposure investigations, rather than controlled laboratory experiments, may then be the only acceptable source of needed information. Chronic

bronchitis did develop over the course of at least one long-term study,[31] however, and various case histories have reported the development of acute and/or chronic respiratory disease after patients endured short- or long-term exposure to H_2SO_4 aerosols.[38, 39]

Definitive data are lacking, but exposure to low concentrations of sulfuric acid appears to increase pulmonary flow resistance in human subjects. Determining the minimum concentration at which such changes might be expected to occur, which is possible for SO_2, is impossible for H_2SO_4. Unfortunately, most experiments on the general complex of sulfur-containing pollutants have dealt with the less toxic sulfur dioxide. Additional work, to be most meaningful, must be conducted by a design that incorporates the refinements of both physiological methodology and aerosol technology. A failure in either of these areas would severely limit the value of the data.

STUDIES OF SENSORY AND CENTRAL NERVOUS SYSTEM RESPONSES TO SULFURIC ACID MIST

In the U.S.S.R., air pollutant limits have been rigidly set by the standard, "that the ambient air should not contain odors to be imposed on the population against its wishes"....[26] With this standard as a guideline, the Russians in the middle fifties conducted studies to limit SO_2 and H_2SO_4 in the air to acceptable levels. The limits finally selected were based on the subjective reactions of human volunteers exposed to either SO_2 or H_2SO_4. The perception threshold for odor and mucosal irritation was about 1.5 mg SO_2/m^3 and about 0.5 mg H_2SO_4/m^3. Subsequent to these studies, in 1957, the Russian government established the allowable single concentrations of SO_2 and H_2SO_4 at 0.5 and 0.3 mg/m^3, respectively - levels one-half to one-third the threshold values.*[26, 40]

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*The term threshold concentration applies to that level of H_2SO_4 aerosol or SO_2 gas that is just perceptible as either odor or irritation. This concentration lies between 0.6 to 0.85 mg/m^3 for the aerosol, and between 1.6 to 2.8 mg/m^3 for the gas.[26, 28, 30, 40, 41] Subthreshold implies that the level of exposure cannot be detected either by odor or by irritation.

Between 1956 and 1962, Russian scientists attempted to define that level of SO_2 and/or H_2SO_4 that could trigger responses in specific receptors of the respiratory system (including the nose). They exposed subjects simultaneously to subthreshold concentrations of SO_2 and H_2SO_4 in an effort to detect responses in the central nervous system (brain). The respiratory receptors, particularly those in the olfactory area, have a well-recognized sensitivity to the action of minimal concentrations of chemical substances that is partially explained by the fact that they are located where the outside air initially comes in direct contact with the internal organism.[26]

The varied responses to H_2SO_4 exposure discussed in this section, although not strictly within the realm of classical toxicology, are included because the data are closely related to the biological considerations of this review. The practical ramifications and toxicological implications of the subsequent neurophysiological responses have not been adequately explored. In addition, one must exercise caution in interpreting such data, since no replicative studies have been made to confirm the reported neurophysiological responses, and informative descriptions of experimental conditions have been less than adequate.[21]

Optical Chronaxy

Alterations in optical chronaxy* following stimulation of the respiratory receptors were examined extensively in hopes of finding the allowable limits of atmospheric pollutants. No change in optical chronaxy was noted when the legal maximum concentrations of SO_2 and/or H_2SO_4 aerosol were administered to volunteers (for H_2SO_4,

*Weak electrical current applied to the eyeball that produces the sensation of a flash of light. Each subject has a maximum intensity of stimulation below which he does not perceive light. The intensity threshold, expressed in units of electrical potential (i.e., volts) is called the rheobase. Chronaxy is the electrical current times twice the intensity that produces the rheobase. A stimulating current of two rheobases causes light sensation only when it is sufficiently prolonged. This value, that is, the time threshold necessary for the appearance of light sensation, is called optical chronaxy.[26]

0.3 mg/m^3; for SO_2, 0.5 mg/m^3); nor when subthreshold concentrations were administered (for H_2SO_4, 0.6 mg/m^3; for SO_2, 1.2 mg/m^3) (Table 1).[30] Exposure to levels of SO_2 or H_2SO_4 beyond threshold consistently elicited increases in the optical chronaxy. When the two irritants were combined, such that the concentration of both was equal to or greater than the subthreshold concentration, the optical chronaxy value indicated an additive or synergistic depression of central nervous system excitation. These data were not sufficient to determine whether the primary response came from the optic cortex itself, or whether a response in the olfactory zone caused a secondary inhibitory effect in the visual cortex, for no changes were detected until concentrations exceeded the odor threshold. Ryazanov[26] has postulated the latter mechanism as a possible explanation for the increased optical chronaxy effect.

Table 1. OPTICAL CHRONAXY ON NINTH MINUTE OF EXPOSURE OF ONE SUBJECT TO TEST ATMOSPHERES[a], [30]

Test gas	Concentration, mg/m^3	Average optical chronaxy, μF
Fresh air	-	0.61 ± 0.0037
SO_2	1.5 to 1.8	0.80 ± 0.0015
SO_2	1.0 to 1.2	0.62 ± 0.0070
H_2SO_4	0.73 to 0.75	0.70 ± 0.0090
H_2SO_4	0.60 to 0.63	0.62 ± 0.0058
SO_2 and H_2SO_4	1.2 and 0.6	0.71 ± 0.0120
SO_2 and H_2SO_4	0.8 and 0.6	0.71 ± 0.0120 (sic)
SO_2 and H_2SO_4	1.2 and 0.4	0.61 ± 0.0100
SO_2 and H_2SO_4	1.5 and 0.75	0.98 ± 0.0280

[a]Results of tests on one subject, Madame B.

Dark Adaptation

Information based on optical chronaxy was substantiated by studies of dark adaptation. The Hagel adaptometer, an instrument that measures changes in light sensitivity of the visual organ while the subject is in darkness, was used, and test subjects were exposed to several concentrations of SO_2 and/or H_2SO_4 aerosol. The average sensitivity of subjects to light was computed from a curve illustrating changes in dark

adaptation with time. The raw data (in relative units) in Table 2[30] show a marked similarity to the data obtained with optical chronaxy techniques. Subthreshold concentrations had no effect on dark adaptation, but levels exceeding threshold reduced adaptation activity in the visual cortex.[26, 30, 42] According to Ryazanov,[26] this effect can also be explained as the result of a primary reflexive response in the olfactory zone that leads to a short period of optical cortex inhibition, which is followed by another, prolonged period of depressed activity in the optical cortex secondary to the influence of reticular formation.[26,43] The second component of this diphasic response was noted in some subjects when their light sensitivity was found markedly depressed 50 to 60 minutes after the dark-adaptation curves had shown post-exposure return toward normal.

Table 2. EYE SENSITIVITY TO LIGHT IN THREE SUBJECTS DURING TWENTIETH MINUTE OF DARK ADAPTATION[30]

Test no.	Concentration of gas added, mg/m³		Average light sensitivity, relative units
	SO_2	H_2SO_4	
	Madame D		
1	0	0	33,400 ± 1,153
2	0.65	0.3	33,200 ± 1,841
3	3.0	0	41,100 ± 1,570
4	0	0.7	42,400 ± 0 (sic)
5	3.0	0.7	54,600 ± 1,200
	Madame P		
6	0	0	54,300 ± 2,857
7	0.65	0.3	55,500 ± 1,385
8	3.0	0	69,300 ± 5,100
9	0	0.7	62,850 ± 3,268
10	3.0	0.7	82,750 ± 1,432
	Madame V		
11	0	0	42,133 ± 972
12	0.65	0.3	41,767 ± 546
13	3.0	0	56,200 ± 3,377
14	0	0.7	54,700 ± 1,570
15	3.0	0.7	68,967 ± 3,050

Continuous Electroencephalography

The Russian scientists next turned to continuous monitoring of the cerebral cortex by electroencephalography (EEG), directly recording the state of central nervous system function during exposure to SO_2 and/or H_2SO_4 aerosols.[40, 43, 44] Mucous membrane irritation, secondary to the sulfur irritation, innervates the trigeminal nerve, while odor perception results from direct excitation of the olfactory receptors. Stimulation of any receptor organs is followed by alpha-rhythm (low-frequency, high-amplitude EEG signal) suppression or desynchronization. Individuals with well-defined alpha rhythms were selected as subjects and the criterion of response was defined as the onset of electrical desynchronization, or alpha-rhythm suppression. Exposing subjects to subthreshold concentrations elicited no electroencephalographic changes, nor did application of both SO_2 and H_2SO_4 at maximal allowable concentrations elicit alpha-rhythm desynchronization, at either beginning or end of exposure. Desynchronization was observed only when threshold doses of H_2SO_4 mist and/or SO_2 were used; then it lasted for 1 to 2 seconds. The H_2SO_4 aerosol changed alpha rhythms only when the concentration was sufficient to be noted subjectively by the volunteers. Subthreshold concentrations, not subjectively perceived, did not appear to alter the central nervous system signals, and, at higher concentrations, the crude subjective indices - odor perception and mucosal irritation - apparently correlated well with the onset of alterations in the central nervous system. Subjective evidence of cortical response was found only when the concentrations were sufficient to affect the course of the other reflex effects (i.e., optical chronaxy and dark adaptation), so that subjective responses apparently were valid as objective indices of the cortical effects of the irritants.

Conditioned Reflexes

An additional physiological concept is referred to in the Russian literature, although apparently not discussed at all in American toxicological studies. According to Gershuni[45] and Dubrovskaya,[41] cortical

reactions may occur upon exposure to certain subthreshold (subsensory) excitations. This may play an essential role in toxicological and health effects. If cortical reactions to subthreshold levels do occur, one must conclude that to be acceptable ambient pollutant levels must not only be below the level of odor perception and irritancy but also below the threshold of subconscious reflex reactions, particularly those capable of altering the functional state of the cerebrum.[25] The electrocortical conditioned reflex is a central nervous system phenomenon elicited only after a succession of repeated, conditioned reflex trials. As indicated previously, temporary desynchronization of the alpha rhythm occurs each time a subject is given a strong light signal. When light is excluded, the alpha rhythm is restored. Experimentally, a system is established by which a subject inhales, for 10 seconds, a known subthreshold concentration of SO_2 gas and/or H_2SO_4 aerosol that by itself does not cause the alpha rhythm to desynchronize. He then receives a light over a 5- to 10-second interval. After repeating this combination (irritant plus light) several many times, desynchronization begins to appear before the light; [illegible]s, apparently in response to the unperceived odor. The unperceived odor thus appears to become the conditioning stimulus, generating the so-called conditioned electrocortical reflex.[26] Through this reflex, EEG alpha-wave desynchronization occurred when individuals were exposed to an H_2SO_4 aerosol concentration of 0.4 mg/m^3, an SO_2 concentration of 0.6 mg/m^3, or to a combination of either 0.15 mg H_2SO_4/m^3 plus 0.5 mg SO_2/m^3, or 0.3 mg H_2SO_4/m^3 plus 0.25 mg SO_2/m^3.[40, 43, 44] All of these concentrations are below the subjective sensory threshold. With respect to H_2SO_4, the conditioned reflex was usually developed in the course of 19 to 23 trials with H_2SO_4 aerosol plus light (Table 3).[40] Remarkable as it may seem, the complex neurological process resulting in disruption of cortical rhythm was initiated by a subjectively nonperceivable odor.[26]

Conclusions

The Russian data are concerned wholly with the effects of H_2SO_4 aerosols upon the interrelationship between sensory modalities and

Table 3. NUMBER OF TRIALS WITH H_2SO_4 PLUS LIGHT REQUIRED FOR APPEARANCE OF CONDITIONED REFLEX[40]

	H_2SO_4 concentration, mg/m^3	
Subject	0.6 to 0.75	0.4
NN	8	23
GV	16	-
SN	12	21
ML	6	19

cerebral cortical function. Those concentrations of H_2SO_4 mist that produce subjective sensations (odor and mucous membrane irritation) were invariably associated with objective evidence of central nervous system depression. Subjective, subthreshold, acid mist concentrations were not associated with depression of either optical chronaxy, dark adaptation, or electroencephalographic patterns. Only when the electrocortical conditioned reflex technique was employed did subthreshold levels result in detectable central nervous system changes. This is evidence that a chemical stimulator, unable to initiate an electroencephalographic response when used in subthreshold doses by itself, can stimulate the central nervous system and change the irritability of cortical cells of the optical and other analytic or cognitive centers when it is used as a conditioning stimulus.[40] Table 4 summarizes the sensory-neurologic dose-response data just described.[44]

Table 4. THRESHOLD AEROSOL DOSES REQUIRED FOR SENSORY RESPONSE[44] (mg/m^3)

	Threshold dose		
Response	H_2SO_4	SO_2	H_2SO_4 + SO_2
Perception of odor and irritation of mucosa	0.6 to 0.85	1.6 to 2.8	0.3 + 0.5
Suppression of dark adaptation	0.63 to 0.73	0.92	0.3 + 0.5
Elevation of optical chronaxy	0.73	1.5	0.6 + 1.2
Disruption of alpha rhythms	0.63	0.9	0.3 + 0.5
Conditioning of electrocortical reflex	0.4	0.6	0.15 + 0.5 or 0.3 + 0.25

SUMMARY

Studies of atmospheric chemistry have shown that under certain conditions sulfur dioxide can be converted to sulfuric acid and particulate sulfates. Air quality criteria and standards for sulfur dioxide should, therefore, take into account the irritant potency of these oxidation products, recognizing that both sulfur dioxide and its degradation products can react further with other air pollutant constituents. Additional aerometric and toxicologic research is needed to supplement what little is known of the actual existence in the atmosphere of this group of compounds and of their toxicology.

TOXICITY IN EXPERIMENTAL ANIMALS

Sulfuric acid is a respiratory irritant that in sufficient concentration will cause the death of exposed animals. The guinea pig is the most sensitive species among the common small laboratory animals, followed in decreasing order by mice, rats, and rabbits. The greater sensitivity of the guinea pig results from its greater susceptibility to bronchial and laryngeal spasm, a characteristic that makes the animal useful for some studies of the irritant potential of low concentrations of sulfuric acid, but that makes extrapolation of the results obtained of questionable value in predicting the health effects of sulfuric acid air pollution in man. Experiments to date have shown that concentration is a more important factor than duration of exposure in producing death in animals.

Sulfuric acid also produces pathological changes in lungs. The degree of lung damage observed after effective, short exposures (up to 72 hours) is related to the mathematical product of concentration and time (CT) rather than to concentration alone. Sulfuric acid damage is repaired slowly. Concentrations below 2 mg/m^3 produce only minor lung damage after extended exposures (about 3 months), which indicates

that the CT relationship observed in 8- and 72-hour exposures cannot be extrapolated directly to long-term effects of low concentrations.

The particle size of sulfuric acid mist seems to be another important factor in determining its irritant potency. When the potency criterion was mortality resulting from an 8-hour exposure, a mist of larger particles (2.7 μm versus 0.8 μm) was more toxic. When pathological lung damage resulting from long-term exposures was the criterion, the effect of 0.9-μm particles was greater than that of either 0.6- or 9-μm particles.

Studies of pulmonary function in animals exposed to these substances cannot be extrapolated simply and directly to predict the human response. They are, however, providing useful information regarding the nature of mechanisms by which effects are produced, and may yet lend insight into responses that are more analogous to the responses of sensitive individuals in the population than of healthy. For practical considerations, these experiments present two principles for indirect guidance in the area of air pollution research. First, because particle size plays an important role in determining irritant potency of sulfur oxide particulates (submicron particles being more irritant), data on mass concentration alone are insufficient for predicting irritant potency. The second important point is that the particulate oxidation products of sulfur dioxide have a generally much greater irritant potency than sulfur dioxide gas per se. This is indicated by comparative data as well as by increases in response to sulfur dioxide in the presence of particulate materials that are known to dissolve the gas and/or to catalyze its conversion to sulfuric acid or sulfates. Along with factors such as the original particle size, presence of other materials in the inhaled air, the subject's breathing pattern, and the site of particle deposition, the hygroscopic nature of sulfuric acid and certain sulfate aerosols affects physiologic responses to their inhalation. Atmospheric levels of sulfur dioxide and the implication of these levels for health should thus be assessed in terms of their potential for forming more irritant substances. To do otherwise would be to miss the toxicological point and seriously becloud important issues.

TOXICITY IN MAN

The combined effects of particle size and concentration of H_2SO_4 mist on exposed human subjects have still not been determined. The effects of temperature and humidity on the response in humans to H_2SO_4 have not been satisfactorily examined either. Long-term human exposure information is, by necessity, limited to epidemiological surveys. Since controlled long-term experimental exposure of humans cannot ethically be performed, industrial and episodic exposures are the only sources of needed information and should be investigated. One long-term study and various case histories have reported the development of acute and/or chronic respiratory disease following short- and long-term exposure to H_2SO_4 aerosol.

Although definitive data are lacking, animal studies indicate that sulfuric acid should increase pulmonary flow resistance in human subjects. The concentration at which such changes might be expected to occur is, however, impossible to determine. Regrettably, the bulk of the experiments relating to the general complex of sulfur-containing pollutants has dealt with the less irritating sulfur dioxide. More research should now be directed to the other components of the complex.

Russian scientists have been almost entirely concerned with the effects of H_2SO_4 aerosols upon sensory modalities, cerebral cortical function, and their interrelationships. Concentrations of H_2SO_4 mist that resulted in subjective sensory stimulation (odor and mucous membrane irritation) were found to be associated invariably with objective evidence of central nervous system depression. Subjectively determined subthreshold concentrations of acid mist were not associated with depression of either optical chronaxy, dark adaptation, or electroencephalographic alterations. Only when the electrocortical conditioned reflex was used did sensory subthreshold levels produce central nervous system stimulation. This has been taken as evidence that, when used as a conditioning stimulus, a chemical stimulator that is unable to initiate an electroencephalographic response when used in subthreshold doses by itself can stimulate the central nervous system and change the irritability of cortical cells of the optical and other analytic or cognitive centers.

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